

## The Benefits of Continuous Dopaminergic Stimulation in the Long-term Treatment of Parkinson's Disease

a report by

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### Introduction

One of the current hot topics in the treatment of Parkinson's disease (PD) is continuous dopaminergic stimulation (CDS). The interest for this treatment strategy is prompted by the notion that, after a few years of therapy with levodopa – the precursor of deficient neurotransmitter dopamine – the response to the drug is complicated by the onset of motor fluctuations, which are a frequent source of disability for PD patients.<sup>1</sup> In fact, the use of levodopa, the 'magic'<sup>2</sup> gold standard for the relief of PD symptoms, can adequately compensate the clinical picture for only a limited period of time, which corresponds to the early phase of the disease, during which the effect of the drug is completely satisfying and the motor response to the drug exceeds what the half-life and the plasma peak of the drug may theoretically support. Unfortunately, this response vanishes after few years: about 50% of PD patients treated with levodopa for more than five years develop motor complications (see *Figure 1*), which can be described as relatively foreseeable changes of variable duration, from phases of good motor performances to others of inadequate mobility, related to the shortening of the efficacy of each levodopa dose.<sup>3</sup> In some cases, fluctuations can also induce depression, anxiety, tachycardia and sweating, which mostly resolve, together with the motor symptoms, when the positive wave of fluctuation comes back.<sup>4</sup> The neural basis of this phenomenon lies in the modification of striatal dopaminergic stimulation induced by PD and only partially improved by the standard preparations of levodopa. Progression of disease severity,<sup>5</sup> which is the clinical expression of the amount of neuronal loss, greatly influences the time of onset of motor complications, but also age,<sup>6</sup> as well as peripheral factors able to affect levodopa pharmacokinetics, such as gastric emptying, can influence the intestinal absorption of levodopa oral formulations.<sup>7</sup>

### The Basal Ganglia Function is Continuous

In the healthy brain, the dopamine neurons fire

tonically and the concentration of dopamine at the striatal level is constantly maintained.<sup>8,9</sup> Stimuli from the environment, especially if new or important in relation to motivation, can modify the extracellular content of dopamine for minutes or hours; also projections from the cortical areas can induce slower or more tonic release of dopamine, but the healthy brain can do its job without any problem, maintaining a relatively constant concentration of dopamine at the striatal level.<sup>10</sup> The re-uptake capability of dopamine transporter and the autoregulatory mechanisms of dopaminergic neurons are among the main contributors for the maintenance of a constant level of dopamine.<sup>11</sup> All these characteristics make dopamine a prominent transmitter for the stability of basal ganglia function and explain why it is essential for the selection and processing of neuronal activity associated with normal movement.

### Dopamine Function in Basal Ganglia and Parkinson's Disease

As a consequence, it is easy to imagine what the loss of dopamine in PD can imply. After the disease onset and an initial compensatory phase, the dopaminergic denervation of the striatum triggers a cascade of events disrupting the functional organisation of the basal ganglia circuitry, which loosens the capability of selecting and facilitating normal movement.<sup>12</sup> Moreover, restoration of dopaminergic function becomes a problem, because regular levodopa, which has a half-life of about 90 minutes, is unable to restore the physiological function of basal ganglia. This fact is not perceived clinically, at least in the early phase, when the patient treated with levodopa has a good clinical response, often compared to a 'honeymoon' period. However, the striatal dopamine receptors, instead of being continuously stimulated by dopamine, as in physiological conditions, are subjected to changing concentrations of dopamine – related to the typical oscillating profile of levodopa plasma levels – so the basal ganglia become less and less efficient. This



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**Table 1: Complications of Parkinson's Disease Related to Treatment**

<b>Motor fluctuations</b>	<b>Dyskinesia</b>
<i>Wearing-off phenomena</i>	<i>Peak-of-dose dyskinesia</i>
<i>End-of-dose hypokinesia</i>	<i>Biphasic dyskinesia</i> (onset and end of dose)
<i>Early-morning hypokinesia</i>	
<i>Postprandial hypokinesia</i>	
<i>Nocturnal hypokinesia</i>	
<i>Unpredictable on-off fluctuations</i>	

non-continuous, pulsatile stimulation of dopamine receptors has also been studied in animal models of PD. In non-human primates, the administration of short-lasting dopaminergic drugs induces motor complication similar to those found in PD patients.<sup>13,14</sup> Moreover, pulsatile dopaminergic stimulation induces plastic changes at the striatal level, involving modifications of gene and protein expression, possibly associated with the development of motor fluctuations; therefore, an aberrant form of neuronal plasticity, causing remodelling of neuronal contacts and pathways, may play a role in this phenomenon.<sup>15-17</sup> It should also be noted that, with the progression of PD, the loss of dopamine in the pars compacta of the substantia nigra makes the striatal concentration of dopamine more and more dependent on the plasma levels of levodopa and reduces the possibility of dopamine terminals to buffer the fluctuations of the plasma levels of dopamine.

#### **Benefits of Prolonged Dopamine Agonists Stimulation in Parkinson's Disease**

The development of motor complications with the administration of short-lasting levodopa was clear after few years of use of this drug, which, when introduced in the late sixties, had a spectacular effect on PD. Motor complications can be various (see *Figure 1*), but all are due to the loss of dopamine in the basal ganglia induced by PD and not adequately compensated by the doses and the way of administration of levodopa. The use of drugs directly stimulating the dopamine receptors and having a different half-life promoted studies comparing their administration with levodopa. The comparison clearly shows that dopamine agonists induce a significant delay in the onset of motor complications, both dyskinesias and fluctuations, but with a weaker clinical efficacy than levodopa.<sup>18-20</sup> The fact that the difference is made by prolonged stimulation can also be argued by the studies showing that a short-acting dopamine agonist like apomorphine rapidly induces dyskinesia if injected, in non-

human primates, as a bolus, and does not if administered by continuous infusion.<sup>21,22</sup> In the same way, chronic levodopa administration to 6-hydroxydopamine-lesioned rats in a pulsatile<sup>23</sup> or continuous way<sup>24</sup> does or does not induce motor fluctuation.

#### **Prolonged Dopamine Agonists Stimulation is Possible using Different Ways of Administration**

The search for therapeutic strategies that may circumvent the problems posed by long-term treatment with levodopa has led to the wide use of dopamine agonists as first choice treatment.<sup>18-20</sup> This, however, may not be enough: optimising the pharmacological treatment of PD should include additional steps, such as improving the clinical effect of dopamine agonists and extending the too-short effects of levodopa.

As for dopamine agonists, the use of alternative routes of administration has shown good clinical results. Apomorphine and lisuride, given subcutaneously with a pump mostly for waking time, allowed good motor performances without motor fluctuations for many years.<sup>25,26</sup> Both these dopamine agonists have a very short half-life and the difference is made by their continuous administration. Obviously, this route of administration may not be suitable for all patients; thus, other ways are being explored: for example, a patch containing a new dopamine agonist, rotigotine, to be applied every 24 hours, is now available.<sup>27</sup> In conclusion, the different formulations of dopamine agonists can provide a continuous dopaminergic stimulation, which is associated with less or no motor fluctuation; the debate about their benefits must take into account the ratio between clinical efficacy and their side effects, which are mainly of the psychiatric type.<sup>28</sup>

As far as prolonging levodopa effects is concerned, continuous levodopa delivery by intra-intestinal infusion during the waking hours, has been proposed and is now available.<sup>29</sup> Also, this mode of administration has proven able to reduce established dyskinesia in PD patients with advanced disease;<sup>30</sup> however, this delivery system, otherwise giving very good clinical results, is not suitable for many patients because its application requires a surgical procedure and surveillance for the potential need of repositioning or replacing the catheter. An attempt to prolong the oral levodopa effect has also been made with slow release formulations of levodopa. An old open study, carried out in long-term treated patients, showed that the sustained release formulation of levodopa

plus benserazide in association with the standard formulation plus benserazide was useful in improving predictable fluctuations.<sup>31</sup> The comparison between the standard formulations and the slow release preparation of levodopa plus carbidopa demonstrated similar levels of control of PD-related symptoms, including fluctuations or dyskinesia, after five years of observation.<sup>32</sup> Another possibility for prolonging the duration of levodopa effect is to add an inhibitor of catechol-O-methyltransferase (COMT) – the catabolic enzyme that converts levodopa into its main metabolite 3-O-methyldopa – thus blocking the metabolism of the drug. COMT inhibitor entacapone, acting on the peripheral metabolism of levodopa, administered every three hours together with levodopa, induced changes in the pharmacokinetic profile of the drug similar to those obtained with continuous infusion.<sup>33</sup> Another COMT inhibitor, more potent than entacapone and also acting within the central nervous system, is tolcapone,<sup>34,35</sup> now available again after having been withdrawn from the market for its potential hepatotoxicity,<sup>36</sup> which may be facilitated by genetic predisposition;<sup>37</sup> frequent controls of liver function are therefore required when using this drug. Other drugs blocking the central metabolism of dopamine are the monoamine oxidase-B

inhibitors (MAOBI), such as deprenyl, which, when proposed as initial treatment, proved able to induce fewer motor complications than levodopa after more than two years;<sup>38</sup> a recent meta-analysis, however, has pointed out that the judgement of MAOBI in early PD requires further large, long-term comparative trials, which include patient-rated quality of life measures.<sup>39</sup>

### Conclusions

Continuous dopaminergic stimulation is currently considered the best therapeutic option for PD. This view is supported by both experimental studies and clinical evidence.<sup>40</sup> Continuous dopaminergic stimulation can be pursued using different approaches, which implies that there are different tools for trying to relieve PD symptoms and for tailoring the best possible therapy for each patient. In fact, if the choice of the therapy is mainly influenced by the disease characteristics, other factors cannot be neglected, including the age of the patient, comorbidities, concomitant use of other drugs and, last but not least, how each patient and his/her family would manage their life with PD. As for ‘when’ continuous dopaminergic stimulation should be started, the obvious answer is: as soon as possible. ■

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